CASE REPORTS

ISONIAZID TOXICITY PRESENTING AS SEIZURES AND METABOLIC ACIDOSIS

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The presenting signs and symptoms of isoniazid toxicity are discussed, with a review of the complications and management of this metabolic encephalopathy with B_6 pyridoxine. This study supports previous studies in finding that ingestion of more than 80 mg/kg body weight produces severe central nervous system symptoms that are rapidly reversed with intravenous administration of pyridoxine.

Key words • isoniazid therapy • isoniazid toxicity • pyridoxine

Isoniazid (INH) therapy has been associated with several adverse central peripheral and hepatotoxic reactions.[1-3] Hepatotoxic effects are age related and induced to a certain extent by the mono-acetyl metabolite.[4] Because INH is the antimycobacterial agent of choice, primarily because of its ability to inhibit mycolic acid synthesis,[5] a select subset of patients will be at risk for developing severe toxic reactions.[6]

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CASE REPORT

A 14-year-old black male was brought to the emergency department on November 23, 1987, with a history of dizziness, vomiting, syncope, and seizures. Drowsiness began approximately 2 hours prior to admission. On admission the patient was semiconscious, confused, and lethargic. During assessment he experienced a seizure. His airway was cleared and oxygen administered, an intravenous line was placed, and 0.9 NaCl was infused. His vital signs revealed blood pressure of 122/60 mmHg, pulse at a rate of 112 beats per minute, and a respiratory rate of 28 breaths per minute. Body temperature was 98.4°F and weight was 46 kg. Blood samples were obtained for hemogram (Table 1), 6/60 profile (Table 2), hepatic enzymes (Table 3), and arterial blood gas analyses (Table 4).

Seizures were treated with intravenous administration of diazepam. In the emergency unit the patient experienced five episodes, each lasting 2 to 2 1/2 minutes. The patient's metabolic acidosis was treated with sodium bicarbonate and blood gases were obtained every hour to determine therapeutic efficacy. The patient's mother reported that the patient was taking INH and B_6 tablets. She expressed concern that he may have taken an overdose of medication. She stated that at least one dozen 300 mg tablets were missing (total 3.6 g). During a period of 30 minutes, 3.6 g of B_6 were infused intravenously (gram/gram of

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TABLE 1. BLOOD COUNT WITH DIFFERENTIAL

WBC 16.5 × 10^3/mm^3
RBC 4.99 × 10^6/mm^3
Hb 14 gram %
Hct 42.2%
MCV 84.6
MCH 28.1
MCHC 33.2
RDW 14.5
PTL 463 × 10^3
Lymphocytes 66%*
Monocytes 6%*
Leukocytes 28%

*Abnormal laboratory values

TABLE 2. ELECTROLYTES, BUN, AND CREATININE PANEL

Sodium 142 mmoL/L
Potassium 3.4 mmoL/L
Chloride 104 mmoL
CO_2 6 mmoL*
BUN 12 Mg/dL
Creatinine 1.3 mg/dL
Glucose 229 mg/dL*
Anion Gap 35 mmoL/L

*Abnormal laboratory values

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INH). Nasogastric intubation and irrigation were carried out, as well as the administration of activated charcoal and magnesium citrate. Three hours forty minutes after admission the patient was markedly improved, oriented, and without seizure activity. He was transferred to the pediatric intensive care unit and recovered completely.

DISCUSSION

The management of overdose cases should proceed in an aggressive but organized manner, with attention to the basic principles of resuscitation in regard to airway, breathing/ventilation, cardiovascular support, and drugs, ie, medications to correct the underlying etiology of the pathology.

The effective management of this case depended on obtaining the history of INH ingestion, recognizing the toxic syndrome associated with this drug, and initiating therapy to correct the toxic process. In reviewing agents that can induce anion gap metabolic acidosis

TABLE 3. ENZYME PROFILE

SGPT (ALT)	37 (3-36) U/L
SGOT (AST)	55 (8-41) U/L
LDH*	334 (9-200) U/L
Alkaline phosphatase*	345 (80-32) U/L
GGTP	17 (15-85) U/L

*Abnormal laboratory values

TABLE 4. ARTERIAL BLOOD GASES RESULTS

	1	2	3
pH	6.69*	6.90*	7.33
PCO_2 (mmHg)	43	36	41.2
pAO_2 (mmHg)	85	113	121.4
HCO_3 (mEq/L)	4.8*	6.7*	21.4
BE (mEq/L)	−27.5*	−27.1*	−3.8*
% O_2 Hb	74	92	98

*Abnormal laboratory values

(Table 5), we found the history in this case to be consistent with INH ingestion. The acidosis can be explained not by the PCO_2 but rather by a bicarbonate deficit, which is a pure metabolic acidosis without compensation.

After the airway has been cleared and intubated if necessary, nasogastric intubation should be carried out and activated charcoal administered to bind isoniazid in the gastrointestinal tract because activated charcoal has a high affinity for isoniazid.[7]

The hallmark of encephalopathy is the triad of repetitive seizures mildly responsive to anticonvulsants, metabolic acidosis, and coma, consistent with severe INH ingestion. One complication in this type of overdose reaction is that administering excessive amounts of anticonvulsants may produce severe sedation because of the large amounts required to reduce the threshold for seizures, thereby compounding the situation.

Toxic ingestion of 80 to 150 mg/kg produces seizures, metabolic acidosis, and coma.[8] The ingestion by this patient exceeded 80 mg/kg.

PHARMACOKINETICS

INH is absorbed from the gastrointestinal tract and peak levels of 1 to 7 μg/mL are obtained in 2 hours.[9]

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Elimination of INH and its metabolites occurs in 24 hours.[10] Quantitative serum levels of INH are not readily available and even if they were, treatment of toxic ingestions should not be delayed to obtain serum levels. Anion gap acidosis is the result of inhibition of lactic dehydrogenase enzyme that metabolizes lactic acid to pyruvate[4]; thus, the accumulation of lactate lowers blood pH and produces the acidotic state. The lowest recorded pH of a patient that survived a toxic ingestion of INH is 6.4. In that case, a combined respiratory and metabolic acidosis resulted.[11] Respiratory acidosis can be a major problem resulting from uncontrolled seizures, thus producing a profound acidosis and cardiopulmonary arrest. The treatment of choice for INH toxicity is pyridoxine 1 g/g of suspected INH ingestion as a single bolus. Because the half-life of INH for fast acetylators is approximately 1 hour as opposed to 3 hours for slow acetylators,[14] rapid acetylators will respond to treatment faster. In severe toxic reactions, exchange transfusion,[9] peritoneal dialysis,[10] and hemodialysis[15] have been efficacious in removing this drug from the bloodstream because protein and tissue binding is minimal. In the management of the comatose patient as well as those with status epilepticus, it is recommended that intermittent infusions of pyridoxine 5 g/5 min mixed with 5% to 10% dextrose and water be administered. This infusion can be repeated every 20 minutes. Blood should be typed and crossed in the event that hemodialysis is required.

CONCLUSIONS

Patients ingesting more than 80 mg/kg or 3 grams of INH should be treated aggressively. Ingestion of amounts < 20 mg/kg or 1.5 g should also be treated, but less aggressively. The patient should be observed for at least 4 hours because peak absorption occurs in 2 hours.

TABLE 5. DRUGS INDUCING METABOLIC ACIDOSIS ANION GAP TYPE

Salicylates
Agents causing seizures
INH
Tricyclics
Strychnine
Theophylline
Agent uncoupling metabolism
Cyanide
Carbon monoxide
Ethylene glycol
Iron
Paraldehyde, phenformin, toluene

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